REMARKS

Applicants respectfully request consideration of the application in view of the foregoing amendments and the following remarks.

Claim 9 is amended herein to more particularly point out and distinctly claim the subject matter of the invention and is presented herein for reconsideration. No new matter has been added.

Rejections under 35 U.S. C. § 102

Claims 1-5, 9, and 11 are rejected under 35 U.S.C. § 102(a) as being anticipated by Touze and Coursaget (*Nucleic Acids Research* 26(5): 1317-23 (1998); hereinafter Touze). Specifically, the Office Action alleges that Touze discloses that HPV16 VLPs may be conjugated to either beta-galactosidase or green fluorescent protein (GFP) via a gene construct (citing Touze, page 1320, penultimate paragraph). Applicants respectfully traverse.

To anticipate a claim, a single prior art source must contain every element of the claim. *Kloster Speedsteel AB v. Crucible Inc.*, 793 F.2d 1565, 1571, 230 USPQ 81, 84 (Fed. Cir. 1986). Applicants assert that the cited claims are not anticipated by the disclosure of Touze because each of the claim limitations is not taught therein.

Each of the cited claims require an HPV pseudovirion, defined in the specification and claims as a virus-like particle *covalently linked* to a reporter gene construct. The instantly claimed pseudovirions are further described in the Specification, on page 2, lines14-16, as a VLP "which is chemically linked or bonded to a reporter gene construct, either directly or through a linking group." Although Touze describes a VLP-reporter combination that they call a "pseudo-virus" (see page 1317, column 2, second full paragraph), it fails to teach a VLP covalently linked to a reporter gene, as described in the instant application. Instead, Touze teaches a virus-like particle which contains a plasmid carrying either a GFP or β-galactosidase reporter gene encapsidated therein. Touze obtains their VLP-reporter combination by expressing recombinant HPV16 L1 in Sf21 insect cells, purifying the resulting wild-type VLPs, disassembling the VLPs into component capsomeres, adding plasmid DNA, and reassembling the VLPs in a buffer containing 5mM $CaCl_2$ and 1% DMSO. The result of this process is a synthetic gene vector system wherein a HPV VLP is able to "package" foreign plasmid DNA *in vitro*.

Contrary to the pseudovirion described in the instant claims, in which a reporter gene construct is covalently linked to a VLP, the pseudo-virus of Touze comprises a VLP in which a reporter plasmid is encapsidated within the structure of the VLP. As such, Applicants respectfully assert that the cited claims are novel over the teachings of Touze and Coursaget. Accordingly, Applicants submit that claims 1-5, 9, and 11 are in condition for allowance and respectfully request that the rejection of these claims under 35 U.S.C. § 102(a) be removed and the claims allowed.

Claims 1-5, 9, and 11 are rejected under 35 U.S.C. § 102(a) as being anticipated by Kawana et al. (*Journal of Virology* 72(12): 10298-10300 (1998); hereinafter Kawana). Specifically, the Office Action alleges that Kawana discloses that HPV16 pseudovirions containing marker plasmids would be potentially useful in developing methods to assay virus-neutralising antibodies and to transfer exogenous genes to HPV-susceptible cells. Applicants respectfully traverse.

Similar to the disclosure of Touze, Kawana fails to teach a VLP covalently linked to a reporter gene, as described in the instant application. Like Touze, Kawana uses the name "pseudovirion" to refer to an HPV VLP that has been disassembled and reassembled in the presence of plasmid DNA, resulting in a VLP with foreign DNA encapsidated therein. Although the "pseudovirions" of the present invention share the same nomenclature as those described by Touze and by Kawana, they are distinctly different in that the reporter gene construct of the present invention is covalently linked to the VLP and not encapsidated therein.

From the above discussion, it is evident that Kawana fails to disclose the pseudovirions of the present invention, and, as such, Applicants respectfully assert that the rejection of claims 1-5, 9, and 11 under 35 U.S.C. § 102(a) is improper. Accordingly, Applicants respectfully request that the rejection of these claims be removed and the claims allowed.

Claims 1-5, and 9-11 are rejected under 35 U.S.C. § 102(e) as being anticipated by Lowy et al. (U.S. Patent No. 6,599,739 B1; hereinafter Lowy). Specifically, it is alleged that Lowy teaches HPV16-BPV1/beta-galactosidase pseudotyped virions. It is also stated that Lowy discloses testing for neutralizing antibodies against HPV16 by mixing HPV16-BPV1/beta-galactosidase pseudotyped virions with a sample from a vaccine to monitor protection from HPV16 infection by an immunoprophylactic vaccine. Applicants respectfully traverse.

Again, like Touze, Lowy fails to disclose the pseudovirions of the present invention, which require a VLP covalently linked to a reporter gene construct. The "pseudotyped virions" of Lowy instead comprise a VLP with foreign DNA encapsidated within its structure, unlike the present invention. Example 5 of Lowy, which was specifically cited in the Office Action, describes an HPV16 VLP with a modified bovine papillomavirus (BPV) genome encapsidated therein, the modified BPV genome comprising a BPV genome in which most of the viral genome has been removed and replaced with a βgalactosidase expression cassette. The remainder of Lowy is also deficient in disclosing a VLP with a reporter gene construct covalently attached.

Applicants respectfully assert that the cited claims are novel over the teachings of Lowy. Accordingly, Applicants submit that claims 1-5, and 9-11 are in condition for allowance and respectfully request that the rejection of these claims under 35 U.S.C. § 102(e) be removed and the claims allowed.

Rejections under 35 U.S.C. § 103

Claims 6-8 and 10 and 12 are rejected under 35 U.S.C. §103(a) as being unpatentable over the teachings of Touze and Coursaget or Kawana et al. Specifically, the Office Action alleges that the disclosures of Touze and Kawana fail to teach the instantly claimed reporter gene construct:VLP ratio, but said ratio is an obvious modification related to establishing optimal reaction conditions. The Office Action also states that Touze and Kawana fail to teach a beta-lactamase gene construct as required by claim 12, but that it would have been obvious to one of skill in the art to substitute a beta-lactamase gene for the beta-galactosidase gene of Touze or Kawana. Finally, the Office Action states that Touze and Kawana teach an assay to determine if anti-HPV neutralizing antibodies are present in mouse serum and allege that it would have been obvious to develop a similar assay to detect anti-HPV neutralizing antibodies in human serum, given the disclosure of Kawana. Applicants respectfully traverse.

Applicants note that the initial burden of presenting a prima facie case of obviousness rests on the Examiner. *In re Oetiker*, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992). To establish a prima facie case of obviousness, the Office Action must show: (1) a suggestion or motivation in the prior art to modify or combine references; (2) a reasonable expectation of success and (3) that all of the claim limitations are taught or suggested by the prior art. MPEP § 2143. Only after a proper prima facie case of obviousness is established does the burden of rebutting the same shift to the Applicants.

In the present case, Applicants assert that the Office Action has failed to establish a prima facie case of obviousness because all of the claim limitations are not taught or suggested by the prior art. Although both Touze and Kawana discuss what they refer to a "pseudovirions," neither article discloses a VLP covalently linked to a reporter gene construct, as required by all of the rejected claims. As discussed above, both Touze and Kawana teach a VLP with a plasmid DNA encapsidated therein, which is very different than the pseudovirions of the instant invention.

Moreover, it is not alleged in the Office Action that the disclosure of Touze or the disclosure of Kawana contains a suggestion to develop a VLP with a reporter gene construct covalently attached, as required by the instant invention. Indeed, Applicants respectfully submit that the disclosure of Touze actually teaches away from the present invention because the focus of their work is to utilize a VLP as a synthetic gene vector system suitable for encapsidating foreign DNA and delivering it to a cell. The focus of the present invention, on the other hand, is the development of an assay to determine if anti-HPV neutralizing antibodies are present in a sample, using HPV pseudovirions.

As stated above, the Office Action alleges that the disclosures of Touze and Kawana fail to teach the reporter gene construct:VLP ratio, as required by claims 6-8, but said ratio is an obvious modification related to establishing optimal reaction conditions. In response thereto, Applicants note that claims 6-8 describe specific reporter gene construct:VLP ratios of specific pseudovirions which comprise a VLP, a heterobifunctional crosslinker, and a reporter gene construct. Touze and Kawana, on the other hand, fail to teach a pseudovirion comprising a heterobifunctional crosslinker; therefore, the instant claims are not merely representative of the development of "optimal reaction conditions" for a construct disclosed in the prior art.

The Office Action also states that Touze and Kawana fail to teach a beta-lactamase gene construct as required by claim 12, but that it would have been obvious to one of skill in the art to substitute a beta-lactamase gene for the beta-galactosidase gene of Touze or Kawana. As previously stated, Touze and Kawana fail to teach a pseudovirion comprising a VLP covalently linked to a reporter gene construct. Therefore, if one of skill in the art were to substitute a beta-lactamase gene for the beta-galactosidase gene in Touze or Kawana, they would not arrive at the instantly claimed invention.

Finally, the Office Action states that Touze and Kawana teach an assay to determine if anti-HPV neutralizing antibodies are present in mouse serum and allege that it would have been obvious to develop a similar assay to detect anti-HPV neutralizing antibodies in human serum, given the disclosure of Kawana. Again, Applicants note that neither Touze nor Kawana teach the pseudovirions of the present invention, which comprise a VLP covalently linked to a reporter gene construct. As such, it is evident that these disclosures do not teach an assay that is similar to the instant neutralization assay, even if human serum were used instead of mouse serum. The assay of the present invention for detecting anti-HPV neutralizing antibodies in a sample is advantageous compared to other assays in the art because of the ease of modification and manipulation of the novel pseudovirions. Both the VLP type and the reporter gene constructs of the pseudovirions of the present invention can be produced easily and modified according to the parameters of the desired assay.

Applicants therefore assert that Claims 6-8, 10, and 12 are not obvious over the prior art teachings of Touze or Kawana. Accordingly, Applicants respectfully request that the rejection of these claims based upon 35 U.S.C. § 103 be removed and the claims allowed.

Summary

It is believed that the claims are in a condition for allowance and a favorable action on the merits is earnestly solicited.

If the Examiner believes that a telephone conference would be of value, she is requested to call the undersigned attorney at the number listed below.

Any additional fees required in connection with this submission may be taken from Merck Deposit Account No. 13-2755.

Respectfully submitted,

By _____

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Date: June 14, 2005